The addition of chemoradiation to lymph node positive gastric cancer is associated with improved overall survival

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Dedication

This project is dedicated to all my clinical and academic mentors and colleagues, whom without their dedication to me I would not be where I am today.

Abstract

Background: Adjuvant therapies improve survival in gastric cancer; however, the role of adjuvant chemoradiation in the treatment of lymph node (LN)-positive gastric cancer remains uncertain. This study sought to determine the role of adjuvant chemoradiation in addition to chemotherapy after resection for lymph node positive gastric cancer.

Methods: The Surveillance, Epidemiology and End Results-Medicare linked data from 2004-2013 was used to identify patients aged 66 and older with LN-positive gastric adenocarcinoma. Multivariable logistic regression evaluated factors associated with receipt of chemoradiation. The Kaplan-Meier method and Cox proportional hazards modeling were used to evaluate overall survival (OS).

Results: A total of 2,409 patients with LN-positive gastric adenocarcinoma who underwent upfront surgical resection were identified; 309 (13%) received adjuvant chemotherapy and 407 (17%) received adjuvant chemotherapy and chemoradiation. Among all patients, median OS was 15 months. Median OS was 20 months for patients who received chemotherapy alone and 27 months for patients who received chemotherapy and chemoradiation ($p<0.05$). Recent diagnosis, older age, tumor stage T3 or T4, and Charleston Comorbidity Index were associated with an increased hazard ratio for death ($p<0.05$). Receipt of chemoradiation was associated with a decreased hazard ratio for death ($p<0.05$).

Conclusions: In patients with LN-positive gastric adenocarcinoma, the addition of chemoradiation to adjuvant chemotherapy after upfront surgical resection was associated with improved survival irrespective of the extent of lymphadenectomy. These data

suggest chemoradiation should be considered in patients with LN-positive gastric adenocarcinoma.

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Introduction

Gastric cancer is the sixth most frequently diagnosed cancer and the third most common cause of cancer related death worldwide(1). In the United states alone, it has an estimated incidence of 28,000 cases per year with an estimated 5-year survival of only 30%(2). Most patients are diagnosed when the disease is confined to the stomach and surrounding lymph nodes(3), making surgical resection a hallmark of curative intent treatment. Amongst those with localized disease, 5-year survival approaches 70%; however this significantly decreases to 30% with regional disease spread and 5% with distant metastatic disease(3).

Surgical resection is the mainstay of curative intent therapy and includes resection of the involved stomach, lymphadenectomy and anatomic reconstruction of the gastrointestinal tract. As over 50% of patients present with nodal involvement, locoregional recurrence is common (4). Due to the high rates of local, regional and distant recurrence in addition to the poor overall survival seen in gastric cancer, perioperative and adjuvant multi-modality treatments have been explored in an attempt to improve outcomes.

Multiple randomized controlled trials have evaluated the role of adjuvant and perioperative therapy in addition to surgical resection(5-10). Chemotherapy and chemoradiation have both been shown to benefit patients with gastric cancer(7, 11, 12). The randomized controlled trial, Intergroup 0116 trial(11, 12), and a subsequent meta-analysis(13) have shown that chemoradiation improves overall survival in resected gastric cancer. Two other randomized controlled trials established a survival and disease-

free survival benefit to adjuvant chemotherapy compared to surgery alone(9, 10, 14). Notably, these trials were based in Japan and Korea, where an extensive D2 lymph node dissection is the standard of care(9, 10, 14). Despite many clinical trials, the optimum adjuvant treatment for resected cancer patients is still debated as a large proportion of patients in the Intergroup trial did not receive an extended (D2) lymph node dissection, and adjuvant treatment strategies had classically been compared to surgery alone, not one another. Many consider a D2 lymph node dissection standard of care surgery, and thus postulated that radiation portended a benefit in the setting of inadequate surgery.

The Adjuvant Chemoradiotherapy in Stomach Tumors (ARTIST) trial evaluated patients who received a gastrectomy with a D2 lymphadenectomy and compared the role of adjuvant chemotherapy alone to adjuvant chemotherapy with chemoradiation(5). The trial found no difference in survival between treatment groups; however, on subgroup analysis, the ARTIST trial identified a possible survival advantage in patients with lymph node-positive disease who received chemoradiation in addition to adjuvant chemotherapy(5). In order to further evaluate the role of adjuvant chemoradiation in addition to chemotherapy in patients with lymph node positive disease, the current study used a large national database to further investigate the role of adjuvant chemoradiation following upfront surgical resection of gastric adenocarcinoma in the United States.

Methods

After approval from the University of Minnesota Institutional Review Board, the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data was used to identify patients aged 66 years and older who were diagnosed with gastric adenocarcinoma from 2004-2013. The SEER program registry is an aggregate of 18 distinct geographic cancer registries and represents approximately 28% of the United States population (15). The SEER registry collects patient and tumor characteristics, including age at diagnosis, race, patient sex, primary tumor site, histologic subtype, tumor stage, tumor size, lymph node status, tumor grade, lymph node evaluation, diagnostic confirmation, type of surgery, vital status, and cause of death. SEER-Medicare linked data provides additional information on patient characteristics, demographics, tumor characteristics, treatment including surgical procedures, chemotherapy, and radiation as well as vital status through the Patient Entitlement and Diagnosis Summary File. Medicare claims data for hospitalizations and inpatient procedures are included in the Medicare Provider Analysis and Review and National Claims History files. Claims data for the year prior to diagnosis were used to calculate a Charlson Comorbidity Index (CCI). Cancer was excluded from the CCI, as it is the disease of interest in this study.

Patients were included in this study if they had histologically confirmed lymph node-positive gastric adenocarcinoma, underwent upfront surgical resection and received adjuvant chemotherapy and/or chemoradiation. Patients were excluded if they received any form of neoadjuvant chemotherapy or radiation, had metastatic disease at diagnosis,

had non-adenocarcinoma gastric cancer, had gastroesophageal junction carcinomas, did not undergo surgical resection, had multiple primary malignancies, or were diagnosed by autopsy or death certificate.

Patients who received adjuvant treatment were then divided into two cohorts, those who received adjuvant chemotherapy alone and those who received adjuvant chemotherapy and chemoradiation. Survival analysis for patients in both cohorts excluded patients who died within the first 3 months after diagnosis, based on the assumption that these patients had undiagnosed distant metastases or were too ill to receive a full course of treatment for their disease.

Comparative statistics were used to analyze differences between demographic, tumor and treatment characteristics across patients in the two cohorts. Multivariable logistic regression analysis was performed to determine factors associated with receipt of chemoradiation. Survival was analyzed using the Kaplan-Meier method and Cox proportional hazard models. All Cox proportional hazard models included year of diagnosis, patient age, gender, race, tumor T-stage, number of lymph nodes examined, CCI, and type of adjuvant treatment. Results were considered statistically significant at a two-tailed p-value ≤ 0.05. All statistical analyses were performed with SAS software, version 9.3 (SAS Institute, Cary, NC). Sensitivity analyses were performed using the SEER database to ensure observed effects were not a product of older patient selection (SEER-Medicare). This analysis was performed using R software (R Foundation for Statistical Computing, Vienna, Austria, 2017).

Results

A total of 2,409 patients were identified in the SEER-Medicare linked data set with lymph node positive gastric adenocarcinoma who underwent upfront surgical resection (Table 1). The median age of the cohort was 73 (interquartile range [IQR] 69-77) and most patients were non-Hispanic white (56%). The majority of patients had T1 and T2 tumors (61%). The median number of lymph nodes examined was 15 (IQR 9-23) and the median number of positive lymph nodes was 4 (IQR 2-9). Among all patients, 1,693 (70%) did not receive any adjuvant therapy, 309 (13%) received chemotherapy alone, and 407 (17%) received adjuvant chemotherapy and chemoradiation. Patient and treatment characteristics for those who received adjuvant treatment are included in Table 2. Patients who received chemotherapy and chemoradiation were younger than those who received chemotherapy alone ($p=0.02$). The median number of positive lymph nodes was 5 (IQR 2-10) for those treated with chemotherapy and 4 (IQR 2-8) for those who received chemotherapy plus chemoradiation.

Multivariate regression was performed to evaluate patient factors associated with the receipt of chemoradiation among all patients with lymph node positive disease (Table 3). Patients were less likely to receive chemoradiation if they were diagnosed in the more recent time period (2009-2013 compared to 2004-2008, $p<0.05$) or were older (75-79 compared to 66-69; 80-84 compared to 66-69; ≥ 85 compared to 66-69, $p<0.05$). Patient gender, race, geographic location, T stage, CCI, and number of lymph nodes examined were not significantly associated with receipt of chemoradiation.

The median OS for all patients with lymph node positive gastric adenocarcinoma was 15 months. The median OS for patients treated only with adjuvant chemotherapy after surgery was 20 months, and the median OS for patients treated with adjuvant chemotherapy and chemoradiation was 27 months (Figure 1, $p<0.05$). The addition of chemoradiation to adjuvant chemotherapy was associated with improved survival, irrespective of the extent of lymphadenectomy performed (Figure 2). In patients who had less than 15 lymph nodes examined, median OS with chemotherapy alone was 16 months versus 25 months for those treated with chemotherapy and chemoradiation (Figure 2a, $p<0.05$). Among patients who had greater than 15 lymph nodes examined and were treated with chemotherapy, the median OS was 16 months versus 31 months for those treated with chemotherapy and chemoradiation (Figure 2b, $p<0.05$).

A Cox-proportional hazards regression model was performed to further evaluate survival while adjusting for other patient factors (Table 4). More recent year of diagnosis (2009-2013 compared to 2004-2008), older age (75-79 compared to 66-69; ≥85 compared to 66-69), increased comorbidities (CCI of 1 compared to 0), and not receiving any adjuvant therapy (compared to chemotherapy alone) were all associated with a significant increase in the hazard ratio for death ($p\leq0.05$). Non-white race and receipt of chemoradiation (compared to chemotherapy alone) were associated with a decreased hazard ratio for death ($p\leq0.05$). The number of lymph nodes evaluated approached significance; in patients with greater than 15 lymph nodes evaluated the hazard ratio for death was 0.91 (95% confidence interval 0.83-1.0, $p=0.05$).

For all models, we performed several sensitivity analyses to ensure that the observed effects were not a product of the older patient selection inherent to utilizing the SEER-Medicare database. We utilized the SEER database to replicate our findings among patients of all ages diagnosed with lymph node positive gastric adenocarcinoma. For these analyses 5,063 patients were identified in the SEER database who underwent upfront surgical resection for lymph node positive stage I-III gastric adenocarcinoma. Of these, only 2,829 received adjuvant chemotherapy and were included in the subsequent sensitivity analyses. Under all assumptions, the conclusions remained unchanged (Appendix A).

Discussion

The current study used a large national database to evaluate the role of adjuvant chemoradiation in patients with lymph node-positive gastric cancer who underwent surgical resection. Notably, 70% of patients did not receive any adjuvant therapy after surgical resection. Patients were less likely to receive chemoradiation if they were older or diagnosed in the more recent time period (2009-2013 compared to 2004-2008). The median OS for the entire cohort of patients diagnosed with lymph node-positive gastric cancer who underwent upfront resection was 15 months. The receipt of adjuvant chemotherapy alone was associated with an improvement in median OS to 20 months, and 27 months for those who received adjuvant chemotherapy and chemoradiation. On multivariable regression analysis, the addition of chemoradiation to adjuvant chemotherapy was associated with a reduction in the hazards ratio for death.

Previous RCTs have demonstrated improved survival with the receipt of adjuvant or perioperative chemotherapy or chemoradiation following surgical resection of gastric adenocarcinoma (5-8, 10-12, 14). In the INT-0116 trial, patients were randomized adjuvant chemoradiation or observation alone after surgical resection(11). Those who received adjuvant chemoradiation had improved OS and locoregional recurrence compared to patients who treated with surgery alone, which persisted after more than 10 years of follow-up (11, 12). The MAGIC trial established the benefit of perioperative epirubicin, cisplatin and fluorouracil over resection alone in gastric adenocarcinoma but did not evaluate the role of chemoradiation(7). While these trials have helped to define treatment algorithms for patients with resectable gastric adenocarcinoma, the role of

adjuvant chemoradiation in the setting of modern adjuvant chemotherapy remained uncertain.

Two subsequent trials have attempted to examine the role of adjuvant chemoradiation in addition to chemotherapy. The ARTIST and CRITICS trials examined whether patients benefited from chemoradiation in addition to chemotherapy after surgical resection (5, 6, 8). The ARTIST trial found no improvement in disease-free survival (DFS) with the addition of chemoradiation (5, 6). However, post-hoc subgroup analysis of patients with nodal metastases found that there was improved 3-year DFS for those treated with chemotherapy plus chemoradiation versus chemotherapy alone after resection (77.5% and 72.3%, respectively, p=0.036)(6). The CRITICS trial similarly found no OS benefit to adjuvant chemoradiation following preoperative chemotherapy compared to perioperative chemotherapy alone (8). Unfortunately, the CRITICS trial did not include additional analyses of a lymph node-positive subgroup. The current study used a large national dataset to evaluate this clinical dilemma and found that the addition of chemoradiation to adjuvant chemotherapy was associated with improved survival in patients with lymph node-positive gastric adenocarcinoma.

It is necessary to recognize that an important controversy in the management of gastric adenocarcinoma is the extent of lymphadenectomy performed during resection. The two major types of lymphadenectomy in gastric cancer are a less extensive D1 lymphadenectomy and a more D2 lymphadenectomy (28). A D2 dissection has become the most widely recommended surgery internationally for resectable gastric cancer and has been shown to lead to a reduction in gastric-cancer specific deaths(16, 28, 29). In

Asia, where the incidence of gastric adenocarcinoma is greater, most surgeons perform a more extensive, D2 lymphadenectomy due to improved oncologic outcomes, while many surgeons in North America and Europe perform a less extensive D1 dissection. In the Western population, the Dutch Gastric Cancer Trial compared D1versus D2 lymphadenectomies and found that the D2 dissection was associated with significantly higher postoperative morbidity and mortality and no difference in OS at 5-years (4, 16-18). However, longer term follow-up at 15 years demonstrated that D2 lymphadenectomy was associated with a significantly decreased risk of death from gastric adenocarcinoma (4). The United Kingdom Medical Research Council similarly performed a randomized trial of D1 versus D2 lymphadenectomies across Europe and found significantly higher in-hospital mortality in the D2 group but no difference between groups in OS at 5 years(19). A more recent Italian study found comparable rates of morbidity, mortality and reoperation between patients receive a D1 and D2 lymphadenectomy, with rates comparable to those seen in the Japanese series (20). These improvements in surgical outcomes may be due to an increase in pancreas and spleen preserving lymphadenectomies in additional to technical improvements by surgeons. Importantly, however, it should be noted that in these trials, chemotherapy and chemoradiation were not included in the treatment protocols. With time, the D2 lymphadenectomy appears to be less morbid of an operation.

Extent of lymphadenectomy was a criticism of the INT-0116 study, in which only 10% of patients received the planned D2 dissection, 36% of patients received a D1 dissection, and 54% received a D0 dissection (12). In that study, chemoradiation may

have compensated for suboptimal surgical therapy, which could explain the observed survival benefit attributed to chemoradiation. In the ARTIST and subsequent ARTIST-II trials, a D2 dissection was an inclusion criterion for the study, as the studies were based in Korean centers where it is standard of care. The results of the present study are based on the SEER-Medicare population in the United States, where a D2 lymphadenectomy is not standard. As the median number of lymph nodes examined was 15, it was unlikely that a high proportion of patients received a D2 lymphadenectomy. Nonetheless, when the survival analysis was stratified by number of lymph nodes examined (<15 versus ≥ 15), the association between improved survival and chemoradiation persisted in both groups, suggesting a benefit to radiation irrespective of extent of dissection. Furthermore, the likelihood of receiving chemoradiation was not associated with the number of lymph nodes examined, suggesting that chemoradiation was not used to compensate for extent of lymphadenectomy.

Importantly, this analysis of the SEER-Medicare database found that 70% of patients who underwent upfront surgical resection for LN-positive gastric adenocarcinoma received no adjuvant treatment, despite several RCTs demonstrating the advantage of multi-modality treatment in addition to surgical resection (5-11). This finding corroborates a previous review of the SEER-Medicare linked data from 2002-2009, which found that only 38.6% of patients with stage III gastric adenocarcinoma received evidence-based care with appropriate adjuvant therapy (21). A similar review of the National Cancer Database found that 30.9% of patients did not receive any adjuvant chemotherapy or radiation, and that the use of radiation decreased throughout the study

period (2006-2013)(22). The present study demonstrated a similar trend of decreased utilization of chemoradiation in the United States over the course of this study (2004-2013).

It is important to address some of the limitations of this retrospective study. Use of an epidemiological and administrative dataset such as SEER introduces potential bias from missing data, coding inaccuracies and reporting bias. Additionally, as a retrospective study, we can only draw associations and not determine causality. Furthermore, SEER-Medicare data does not contain specific information on the exact chemotherapy and radiation regimens, resection margin status or the specific locations of the lymph node basins dissected. Thus, while lymphadenectomy is an important component of surgical resection for gastric adenocarcinoma, we can only infer extent of lymphadenectomy from the number of lymph nodes examined. Using the SEER-Medicare dataset, only patients aged 65 years and greater can be evaluated. However, the median age of patients diagnosed with gastric cancer in the United States is 68 years, with more than 60% of patients diagnosed at age 65 or older, so the study population still represents the majority of patients with the gastric cancer (2, 23). Additionally, the findings presented here were replicated in SEER amongst patients of all ages as a part of the sensitivity analyses. Lastly recent RCTs such as the MAGIC trial have shown the benefit to perioperative chemotherapy(7), however in the present study all patients who received neoadjuvant therapy were excluded. While this potentially limits the applicability of the study in an era of perioperative treatment, it is important to note that

only 12-36% of patients actually receive neoadjuvant therapy (24, 25), making this study still applicable for the majority of patients with gastric adenocarcinoma.

In conclusion, in the United States Medicare population, the addition of adjuvant chemoradiation to chemotherapy following upfront surgical resection for lymph node-positive gastric cancer was associated with improved survival. The improved survival associated with chemoradiation persisted irrespective of the extent of lymphadenectomy performed; however, there was a greater associated improvement in median OS amongst those with a more extensive lymphadenectomy. Even after controlling for other relevant patient and treatment factors, the combination of adjuvant chemotherapy and chemoradiation was associated with improved survival. These data suggest that chemoradiation should be considered as a component of adjuvant therapy for patients with lymph node-positive gastric cancer following upfront surgical resection. Further studies, including randomized controlled trials, are needed to more closely define the role of adjuvant chemoradiation in node-positive gastric cancer, particularly with modern multi-modality therapy regimens.

Table 1: Patient characteristics of all patients with lymph node-positive gastric adenocarcinoma age 66 and above in the SEER-Medicare data set from 2004-2013 (n=2,409)

		Patients (%)
Year of Diagnosis		
	2004-2008	1343 (56)
	2009-2013	1066 (44)
Age, year		
	66-69	507 (21)
	70-74	583 (24)
	75-79	540 (23)
	80-84	487 (20)
	≥85	292 (12)
Gender		
	Male	1382 (57)
	Female	1027 (43)
Race		
	Non-Hispanic White	1344 (56)
	Black	302 (12)
	Other or Unknown	763 (32)
Treating Institution		
	Urban	2263 (94)
	Rural	146 (6)
Tumor Stage		
	T1 and T2	1469 (61)
	T3	766 (32)
	T4	174 (7)
Charlson Comorbidity Index		
	0	1259 (52)
	1	624 (26)
	2+	526 (22)
Number of Lymph Nodes Examined		
	<15	1113 (46)
	15+	1296 (54)
Adjuvant Therapy		
	None	1693 (70)
	Chemotherapy	309 (13)
	Chemotherapy + Chemoradiation	407 (17)

Table 2: Patient characteristics of patients with lymph node-positive gastric adenocarcinoma who were treated with adjuvant therapy in SEER-Medicare (2004-2013).

	Chemotherapy and Chemoradiation (n=407) Patients (%)	Chemotherapy (n=309) Patients (%)	p-value
Year of Diagnosis			0.003
2004-2008	268 (66)	170 (55)	
2009-2013	139 (34)	139 (45)	
Age, years			0.02
66-69	138 (34)	80 (26)	
70-74	131 (32)	90 (29)	
75-79	85 (21)	83 (27)	
≥80-84	53 (13)	56 (18)	
Gender			0.99
Male	254 (62)	193 (62)	
Female	153 (38)	116 (38)	
Race			0.63
Non-Hispanic White	235 (58)	183 (59)	
Black	44 (11)	38 (12)	
Other or Unknown	128 (31)	88 (29)	
Treating Institution			0.41
Urban	380 (93)	293 (95)	
Rural	27 (27)	16 (5)	
Tumor Stage			0.24
T1/T2	246 (60)	202 (65)	
T3	137 (34)	86 (28)	
T4	24 (6)	21 (7)	
Charlson Comorbidity Index			0.72
0	221 (54)	161 (52)	
1	110 (27)	83 (27)	
2+	76 (19)	65 (21)	
Number of Lymph Nodes Examined			0.70
<15	181 (44)	133 (43)	
15+	226 (56)	176 (57)	

Table 3: Multivariable logistic regression of factors associated with the receipt of chemoradiation in patients with lymph node-positive gastric cancer in the SEER-Medicare data from 2004-2013.

		Odds Ratio	95% CI	
Year of Diagnosis				
	2004-2008		1.00 Referent	
	2009-2013	**0.56**	**0.44**	**0.70**
Age, year				
	66-69		1.00 Referent	
	70-74	0.79	0.60	1.04
	75-79	**0.47**	**0.35**	**0.64**
	80-84	**0.24**	**0.17**	**0.35**
	≥85	**0.11**	**0.06**	**0.21**
Gender				
	Male		1.00 Referent	
	Female	0.90	0.71	1.13
Race				
	Non-Hispanic White		1.00 Referent	
	Black	0.73	0.51	1.04
	Other or Unknown	0.91	0.71	1.17
Treating Institution				
	Urban		1.00 Referent	
	Rural	0.99	0.64	1.57
Tumor Stage				
	T1 and T2		1.00 Referent	
	T3	1.10	0.87	1.40
	T4	0.77	0.48	1.22
Charlson Comorbidity Index				
	0		1.00 Referent	
	1	1.04	0.80	1.36
	2+	0.94	0.70	1.27
Number of Lymph Nodes Examined				
	<15		1.00 Referent	
	15+	1.05	0.84	1.32

Bold text indicated statistical significance.

Table 4: Cox proportional hazards ratio for death among patients with lymph node-positive gastric adenocarcinoma in SEER-Medicare from 2004-2013.

	Hazard Ratio	95% CI		p-Value
Year of Diagnosis				
2004-2008		1.00 Referent		
2009-2013	**1.56**	**1.41**	**1.71**	**<.0001**
Age, year				
66-69		1.00 Referent		
70-74	1.04	0.90	1.20	0.58
75-79	**1.22**	**1.05**	**1.41**	**0.01**
80-84	1.13	0.97	1.31	0.12
≥85	**1.32**	**1.11**	**1.56**	**0.0001**
Gender				
Male		1.00 Referent		
Female	1.07	0.97	1.17	0.19
Race				
Non-Hispanic White		1.00 Referent		
Black	0.97	0.85	1.12	0.71
Other or Unknown	**0.80**	**0.72**	**0.89**	**<.0001**
Treating Institution				
Urban		1.00 Referent		
Rural	1.03	0.85	1.25	0.74
Tumor Stage				
T1 and T2		1.00 Referent		
T3	**0.71**	**0.64**	**0.78**	**<.0001**
T4	1.14	0.96	1.36	0.14
Number of Lymph Nodes Examined				
<15		1.00 Referent		
15+	0.91	0.83	1.00	0.05
Charlson Comorbidity Index				
0		1.00 Referent		
1	**1.14**	**1.02**	**1.27**	**0.02**
2+	1.12	0.99	1.26	0.07
Adjuvant Therapy				
None	**1.41**	**1.22**	**1.62**	**<.0001**
Chemotherapy Alone		1.00 Referent		
Chemoradiation	**0.77**	**0.64**	**0.92**	**0.004**

Bold text indicated statistical significance.

Figure 1: Kaplan Meier survival curve of patients with lymph node-positive gastric adenocarcinoma, stratified by type of adjuvant treatment. Median survival 20 months for patients treated with chemotherapy and 27 months for patients with chemotherapy and chemoradiation, $p<0.05$.

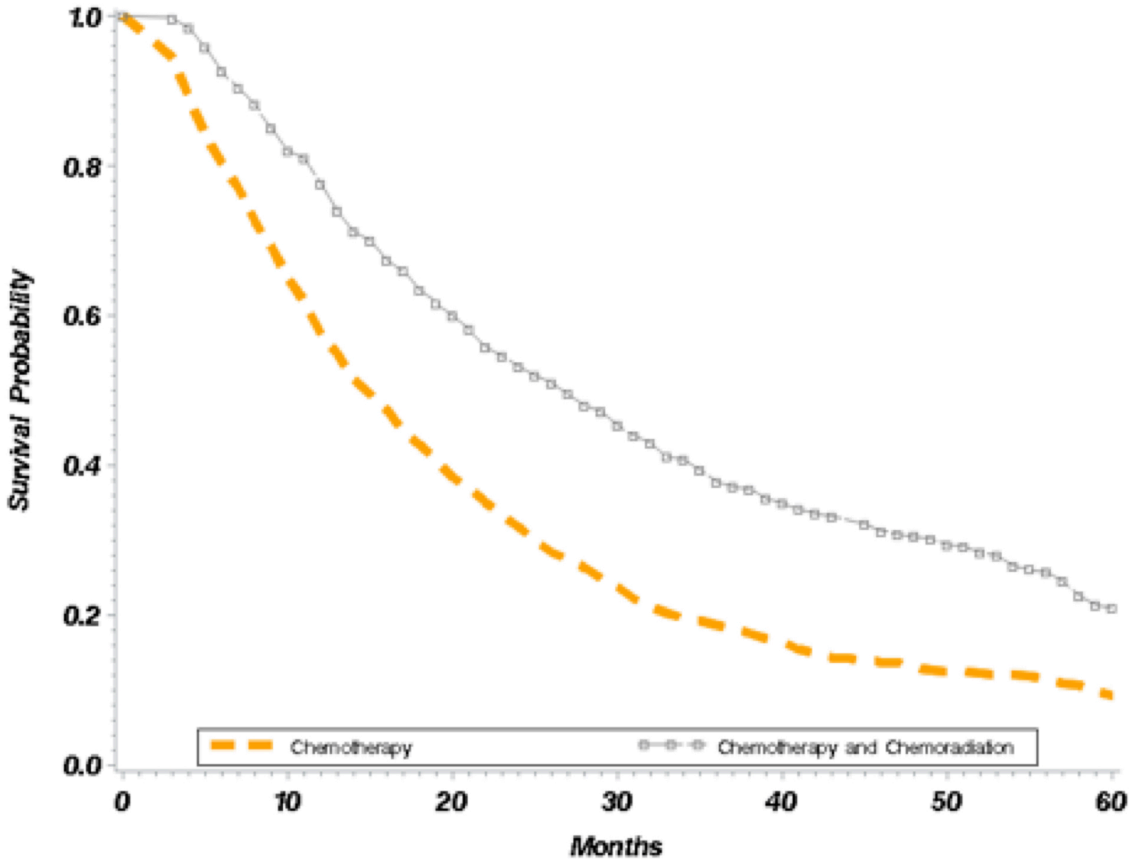
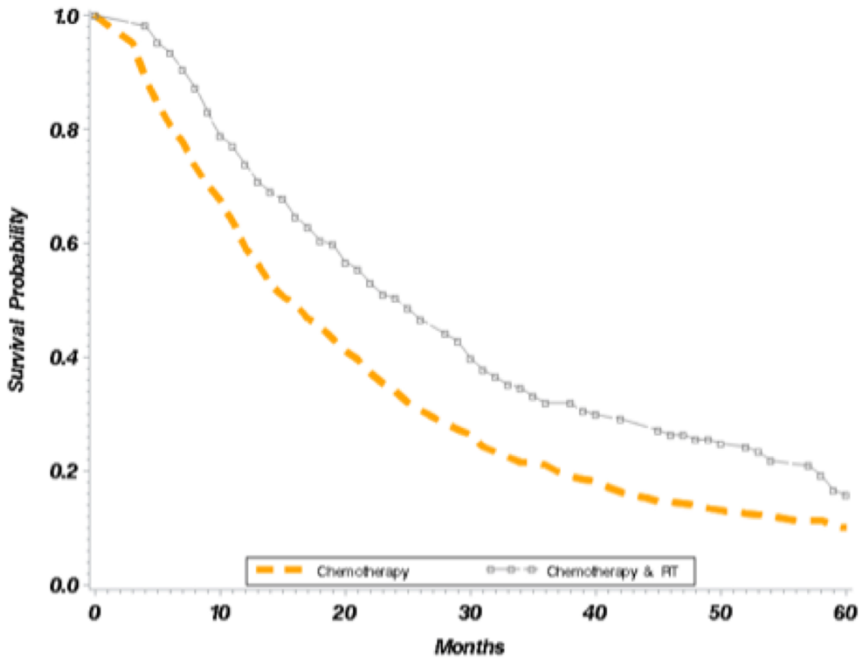
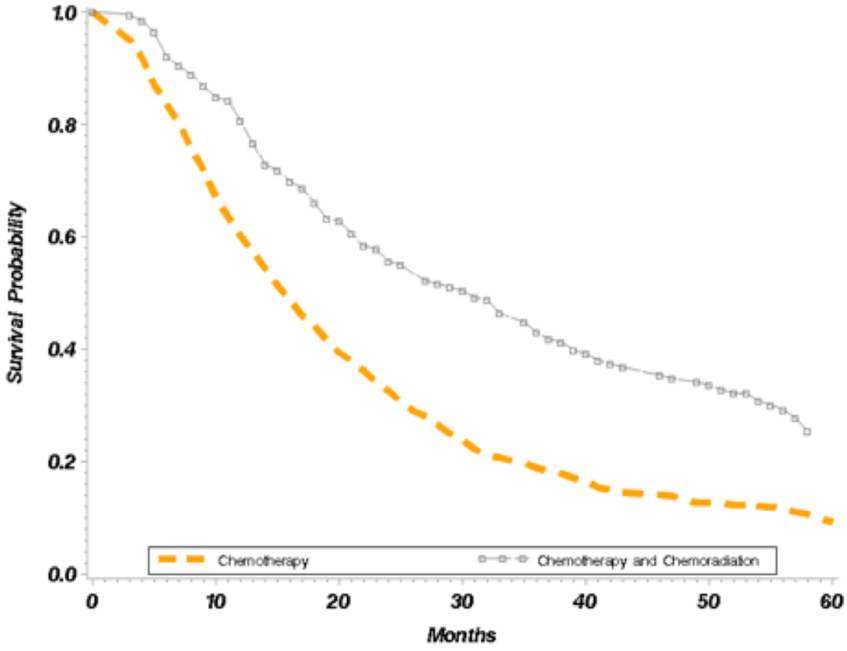


Figure 2: Kaplan Meier survival curve stratified by extent of lymphadenectomy. A) Kaplan Meier survival curve of patients with less than 15 lymph nodes examined treated with chemotherapy or chemotherapy and chemoradiation. Median survival for patients treated with chemotherapy is 16 months and median survival for patients treated with chemoradiation is 25 months ($p<0.05$). B) Kaplan Meier survival curve of patients with 15 or more lymph nodes examined treated with chemotherapy or chemotherapy and chemoradiation. Median survival for patients treated with chemotherapy was 16 months and 31 months for those treated with chemotherapy and chemoradiation ($p<0.05$).

A)



B)


1.0
0.8
0.6
0.4
0.2
0.0
Survival Probability
0
10
20
30
40
50
60
Months
Chemotherapy
Chemotherapy and Chemoradiation

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Appendix

Sensitivity analysis performed in SEER including patients diagnosed with lymph node positive gastric cancer from 2004-2013 who underwent upfront surgical resection and adjuvant chemotherapy.

Table A1: Patient characteristics of SEER cohort

Patient Characteristic		Chemotherapy n=884	Chemotherapy and Radiation n=1945	p
Year of Diagnosis (%)	2004-2008	371 (42.0)	1016 (52.2)	<0.001
	2009-2013	513 (58.0)	929 (47.8)	
Patient Age (%)	10-20	0 (0.0)	2 (0.1)	0.196
	20-29	3 (0.3)	17 (0.9)	
	30-39	49 (5.5)	88 (4.5)	
	40-49	114 (12.9)	261 (13.4)	
	50-59	200 (22.6)	495 (25.4)	
	60-69	239 (27.0)	535 (27.5)	
	70-79	215 (24.3)	434 (22.3)	
	80+	64 (7.2)	113 (5.8)	
Sex (%)	Female	390 (44.1)	850 (43.7)	0.868
	Male	494 (55.9)	1095 (56.3)	
Race (%)	Black	136 (15.4)	354 (18.2)	0.021
	Other	203 (23.0)	513 (26.4)	
	Unknown	3 (0.3)	7 (0.4)	
	White	542 (61.3)	1071 (55.1)	
T Stage (%)	T1	76 (8.6)	158 (8.1)	<0.001
	T2	480 (54.3)	1121 (57.6)	
	T3	296 (33.5)	647 (33.3)	
	T4	8 (0.9)	7 (0.4)	
	TX	24 (2.7)	12 (0.6)	
Number of Lymph Nodes Evaluated (%)	</=15	434 (49.1)	977 (50.2)	0.603
	>15	450 (50.9)	968 (49.8)	
Number of Positive Nodes (mean (sd))		5.53 (4.56)	5.51 (4.22)	0.929

Figure A1: Kaplan-Meier survival curve including all patients with lymph node positive gastric cancer in SEER treated with adjuvant chemotherapy alone or adjuvant chemotherapy and radiation. Median survival 24 months for those treated without radiation and 35 months for those treated with radiation ($p<0.0001$)

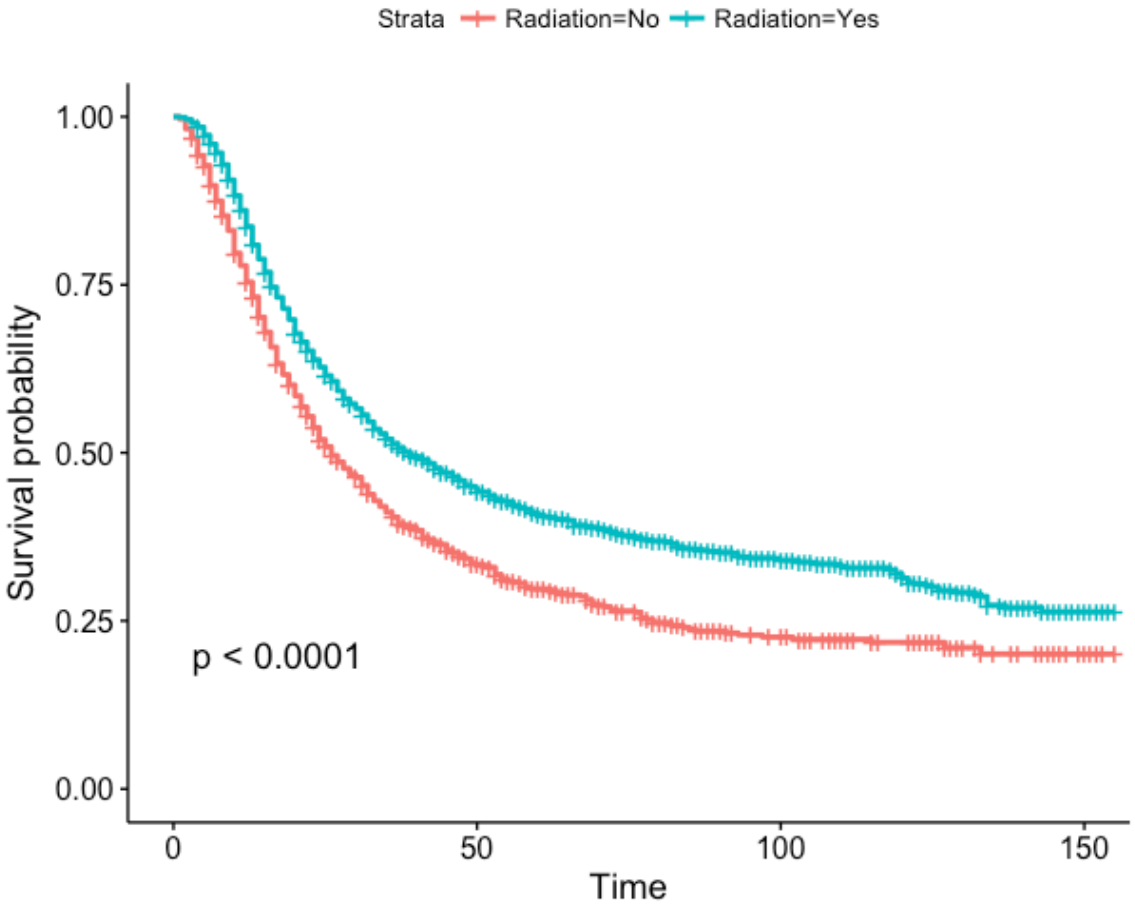
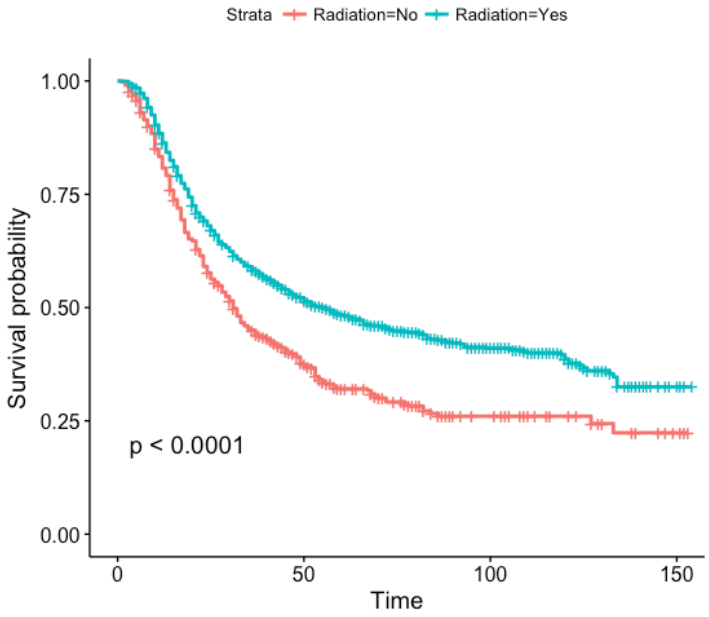


Figure A2: Kaplan-Meier survival curve including all patients with lymph node positive gastric cancer stratified by extent of lymphadenectomy. A) Patients with a lymph node dissection of >15 nodes. Median overall survival was 28 months with chemotherapy alone and 41 months with chemotherapy and chemoradiation (p<0.0001). B) Patients with a lymph node dissection ≤15, median overall survival was 21 months with chemotherapy alone and 30 months with chemotherapy and chemoradiation (p<0.0001).

A)



B)

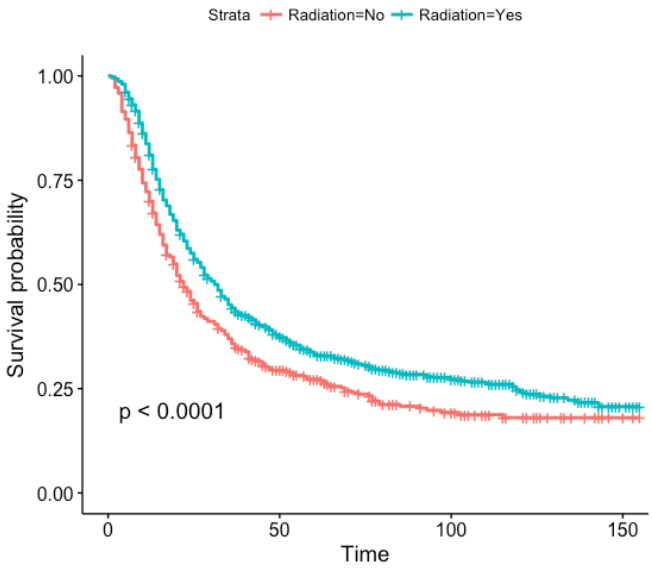

Strata
Radiation=No
Radiation=Yes
1.00
0.75
0.50
0.25
0.00
Survival probability
p < 0.0001
0
50
100
150
Time

Table A2: Cox proportional hazards ratio for death model performed in SEER.

		Hazard Ratio	95% Confidence Interval		p value
Radiation	None	Referent			
	Yes	0.738	0.670	0.814	<0.001
Gender	Male	Referent			
	Female	0.976	0.890	1.071	0.611
T Stage	T1	Referent			
	T2	1.789	1.452	2.203	<0.001
	T3	3.016	2.439	3.731	<0.001
	T4	3.091	1.727	5.533	<0.001
	Tx	2.010	1.291	3.128	0.002
Year of Diagnosis	2004-2008	Referent			
	2009-2013	0.936	0.851	1.030	0.174
Race	Black	Referent			
	Other	0.802	0.694	0.926	0.003
	Unknown	0.131	0.018	0.937	0.430
	White	0.917	0.810	1.038	0.172
Age	10-19	Referent			
	20-29	1.153	0.147	9.047	0.892
	30-39	1.097	0.152	7.915	0.927
	40-49	1.149	0.161	8.220	0.890
	50-59	1.188	0.166	8.486	0.864
	60-69	1.230	0.172	8.788	0.836
	70-79	1.497	0.210	10.697	6.880
	80+	1.794	0.250	12.884	0.561
Nodes Evaluated	</=15	Referent			
	>15	0.703	0.640	0.772	<0.001